

Case fatality rate and viral aetiologies of acute respiratory tract infections in people living with HIV in Africa: The VARIAFRICA-HIV systematic review and meta-analysis

Appendix

Supplementary Tables

Supplementary Table 1 : PRISMA checklist	3
Supplementary Table 2 : Search strategy in PubMed	6
Supplementary Table 3 : Characteristics of included studies	7
Supplementary Table 3 : Individual characteristics of included studies	8
Supplementary Table 4 : Publication bias and Trim-and-Fill adjusted analysis	11
Supplementary Table 5 : Subgroup analysis for comparison of viral aetiologies of acute respiratory tract infections in Africa between HIV positive and HIV negative individuals	12

Supplementary Figures

Supplementary Figure 1 : Funnel plot for publication bias in comparison of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa.....	14
Supplementary Figure 2 : Funnel plot for publication bias in comparison of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa, after Trim-and-Fill adjusted analysis	14
Supplementary Figure 3 : Subgroup-analysis of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa: children aged ≤ 5 years versus people aged > 5 years	15
Supplementary Figure 4 : Subgroup-analysis of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa: children (≤ 15 years) versus adults	16
Supplementary Figure 5 : Subgroup-analysis of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa: by regions in Africa ..	17
Supplementary Figure 6 : Comparison of respiratory viral aetiologies of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa.....	18
Supplementary Figure 7 : Funnel plot for publication for comparison of Human Adenovirus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa	19
Supplementary Figure 8 : Funnel plot for publication for comparison of Respiratory Syncytial Virus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa	19
Supplementary Figure 9 : Funnel plot for publication for comparison of Human Parainfluenza Virus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa	20

Supplementary Figure 10 : Funnel plot for publication for comparison of Human Influenza Virus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa	20
Supplementary Figure 11 : Funnel plot for publication for comparison of Human Metapneumovirus Virus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa.....	21

Supplementary Table 1 : **PRISMA checklist**

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

Supplementary Table 2 : *Search strategy in PubMed*

Search	Search terms
#1	“HIV” OR AIDS OR “Human Immunodeficiency Virus” OR “acquired immunodeficiency virus”
#2	“lower respiratory tract infect*” OR “LRTI” OR “acute lower respiratory infect*” OR “ALRI” OR “pneumonia” OR “community acquired pneumonia” OR “bronchiolitis” OR “severe acute respiratory infect*” OR “severe acute respiratory illness” OR “ILI” OR “Influenza Like Illness” OR “whooping cough” OR “bronchopneumonia” OR “pleurisy” OR “pleuropneumonia” OR “bronchitis” OR “respiratory infect*” OR “upper respiratory tract infect*” OR “upper respiratory infect*”
#3	Africa* OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR "Guinea Bissau" OR "Ivory Coast" OR "Cote Ivoire" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "South Africa" OR “South Sudan” OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe OR "Central Africa" OR "Central African" OR "West Africa" OR "West African" OR "Western Africa" OR "Western African" OR "East Africa" OR "East African" OR "Eastern Africa" OR "Eastern African" OR "North Africa" OR "North African" OR "Northern Africa" OR "Northern African" OR "South African" OR "Southern Africa" OR "Southern African" OR "sub Saharan Africa" OR "sub Saharan African" OR "sub Saharan Africa" OR "sub Saharan African”
#4	#1 OR #2 OR #3
#5	("2000/01/01"[Date - Publication] : "3000"[Date - Publication])

Supplementary Table 3 : *Characteristics of included studies*

Characteristics	N = 36
Publication date	2000-2017
Period of participants recruitment	1994-2016
%Males	38-68 (n = 26 studies)
Mean/median age, years	3 months – 40 years (n = 20 studies)
Design	
- Cross sectional	27
- Clinical trial	4
- Cohort	3
- Case control	2
Setting	
- Urban	4
- Semi-Urban	10
- Rural	3
- Not reported	9
Sampling	
- Consecutive	32
- Random	3
- Systematic	1
Timing of data collection	
- Prospective	30
- Retrospective	6
Clinical presentation	
- Severe form	33
- Severe and benign forms	3
Age groups	
- Children \leq 5 years	21
- All age groups	5
- Adults (> 15 years)	5
- Children (\leq 15 years)	4
- People aged > 5 years	2

Supplementary Table 4 : *Individual characteristics of included studies*

Study	Year	Study Design	Sampling method	Period of data collection	Timing of data collection	Clinical Presentation	Origin of laboratory sample	Mean or Median Age	%Male	Country	Population	Risk of bias
Annamalay, 2016	2016	Cross sectional	Consecutive	Sep/2010–Apr/2013	Prospective study	Severe RTI	Nasal; Pharyngeal	20.7 months	51.6	Mozambique	Children < 15 y	Moderate
Annamalay, 2016	2016	Cross sectional	Consecutive	Jul/2011–Nov/2012	Prospective study	Severe RTI	Nasal; Pharyngeal	7.1 months	67.6	Mozambique	Children < 5 y	Moderate
Cohen, 2015	2015	Cross sectional	Consecutive	2009–2014	Prospective study	Severe RTI	Nasal; Pharyngeal; Throat	NR		South Africa	All ages	Moderate
Cohen, 2015	2015	Cross sectional	Consecutive	Feb/2009–Dec/2013	Prospective study	Severe RTI	Nasal; Pharyngeal; Throat	NR		South Africa	All ages	Moderate
Cohen, 2015	2015	Cross sectional	Systematic	Feb/2009–Dec/2012	Prospective study	Severe RTI	Nasal; Pharyngeal	NR	57.5	South Africa	Children < 5 y	Moderate
Cohen, 2015	2015	Cross sectional	Consecutive	Feb/2009–Dec/2012	Prospective study	Severe RTI	Nasal; Pharyngeal; Throat	NR	39.0	South Africa	People > 5 y	Moderate
Cohen, 2016	2016	Cross sectional	Consecutive	Jan/2010–Dec/2013	Prospective study	Severe RTI	Nasal; Pharyngeal	NR		South Africa	Children < 5 y	Moderate
Feikin, 2012	2012	Cross sectional	Consecutive	May/2007–Feb/2010	Prospective study	Severe RTI	Nasal; Oral; Pharyngeal	12 years	43.0	Kenya	People > 5 y	Moderate
Graham, 2011	2011	Cross sectional	Consecutive	Jul/2005–Nov/2006	Prospective study	Severe RTI	NA	11 months	54.0	Malawi	Children < 15 y	Moderate
Hellferscee, 2017	2017	Cross sectional	Consecutive	Jan/2009–Dec/2012	Prospective study	Severe RTI	Nasal; Oral; Pharyngeal	NR	48.8	South Africa	All ages	Moderate
Ho, 2017	2017	Case control	Consecutive	Apr/2013–Mar/2015	Prospective study	Begnin RTI; Severe RTI	Nasal; Oral; Pharyngeal	33.5 years	51.3	Malawi	Adults	Moderate
Hooli, 2016	2016	Cross sectional	Consecutive	Oct/2011–Jun/2014	Prospective study	Severe RTI	NA	8.7 months	56.3	Malawi	Children < 5 y	Moderate
Jeena, 2006	2006	Cross sectional	Consecutive	Jan/1999–Aug/2001	Prospective study	Severe RTI	NA	17 months	55.7	South Africa, Zambia	Children < 5 y	Moderate
Jeena, 2007	2007	Cross sectional	Consecutive	NR	Prospective study	Severe RTI	NA	17 months	56.0	South Africa	Children < 5 y	Moderate
Kelly, 2015	2015	Cross sectional	Consecutive	Apr/2012–Oct/2013	Prospective study	Severe RTI	NA	6 months	55.0	Botswana	Children < 5 y	Moderate
Lazzerini, 2016	2016	Cross sectional	Consecutive	2001–2012	Retrospective study	Severe RTI	NA	NR	54.0	Malawi	Children < 5 y	Moderate

Madhi, 2000	2000	Cross sectional	Consecutive	Mar/1997–Feb/1998	Prospective study	Severe RTI	NA	8.5 months	57.8	South Africa	Children < 5 y	Moderate
Madhi, 2000	2000	Cross sectional	Consecutive	Mar/1997–Mar/1998	Prospective study	Severe RTI	Nasal	8.5 months	57.2	South Africa	Children < 5 y	Moderate
Madhi, 2006	2006	Cross sectional	Random	March 1998–October 2000	Prospective study	Severe RTI	Nasal	NR		South Africa	Children < 5 y	Low
Madhi, 2007	2007	Cohort	Consecutive	Jan/2000–Dec/2002	Retrospective study	Severe RTI	Nasal; Pharyngeal	NR		South Africa	Adults	Low
Majozi, 2017	2017	Cohort	Consecutive	Dec/2010–May/2015	Retrospective study	Severe RTI	NR	NR	58.9	South Africa	Children < 15 y	Low
Moyes, 2013	2013	Cross sectional	Consecutive	Jan/2010–Dec/2011	Prospective study	Severe RTI	Nasal; Pharyngeal	NR		South Africa	Children < 5 y	Low
Moyes, 2017	2017	Cross sectional	Consecutive	Feb/2009–Dec/2013	Prospective study	Severe RTI	Nasal; Oral; Pharyngeal	NR	38.0	South Africa	Adults	Low
Ngari, 2017	2017	Cohort	Consecutive	Jan/2007–Dec/2012	Prospective study	Severe RTI	NA	8.9 months		Kenya	Children < 5 y	Low
Nunes, 2014	2014	Cross sectional	Random	February 2000 to 31st January 2002	Retrospective study	Severe RTI	Nasal	10 months	57.3	South Africa	Children < 5 y	Low
Nyawanda, 2016	2016	Cross sectional	Consecutive	Sep/2009–Aug/2013	Prospective study	Severe RTI	Nasal; Oral; Pharyngeal	1.4 years	54.0	Kenya	Children < 5 y	Low
Peterson, 2016	2016	Cross sectional	Consecutive	Jan/2011–Dec/2014	Prospective study	Severe RTI	Nasal; Pharyngeal	NR		Malawi	Children < 15 y	Low
Scott, 2000	2000	Cohort	Consecutive	Mar/1994–May/1996	Prospective study	Severe RTI	NA	NR	63.0	Kenya	Adults	Low
Sigaúque, 2009	2009	Cross sectional	Consecutive	Mar/2004–Mar/2006	Prospective study	Severe RTI	NA	8 months	58.0	Mozambique	Children < 5 y	Low
Srinivasan, 2012	2012	Cross sectional	Random	NR	Prospective study	Severe RTI	NA	18 months	56.2	Uganda	Children < 5 y	Low
Sutcliffe, 2016	2016	Case control	Consecutive	NR	Prospective study	Severe RTI	NA	NR	52.8	Zambia	Children < 5 y	Low
Tempia, 2017	2017	Cross sectional	Consecutive	May 2012–April 2016	Prospective study	Begnin RTI; Severe RTI	Nasal; Oral; Pharyngeal	NR		South Africa	All ages	Low
Venter, 2011	2011	Cross sectional	Consecutive	Jan/2006–Dec/2007	Retrospective study	Begnin RTI; Severe RTI	Nasal; Pharyngeal	3 months	52.8	South Africa	Children < 5 y	Low
Yone, 2012	2012	Cross sectional	Consecutive	Jan/2008–May/2012	Retrospective study	Severe RTI	NA	40 years	48.1	Cameroon	Adults	Low
Zar, 2001	2001	Cross sectional	Consecutive	Jan/1998–Dec/1998	Prospective study	Severe RTI	NA	6 months	57.2	South Africa	Children < 5 y	Low

Zash, 2016	2016	Cross sectional	Consecutive	NR	Prospective study	Severe RTI	Nasal	NR		Botswana	Children < 5 y	Low
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Supplementary Table 5 : *Publication bias and Trim-and-Fill adjusted analysis*

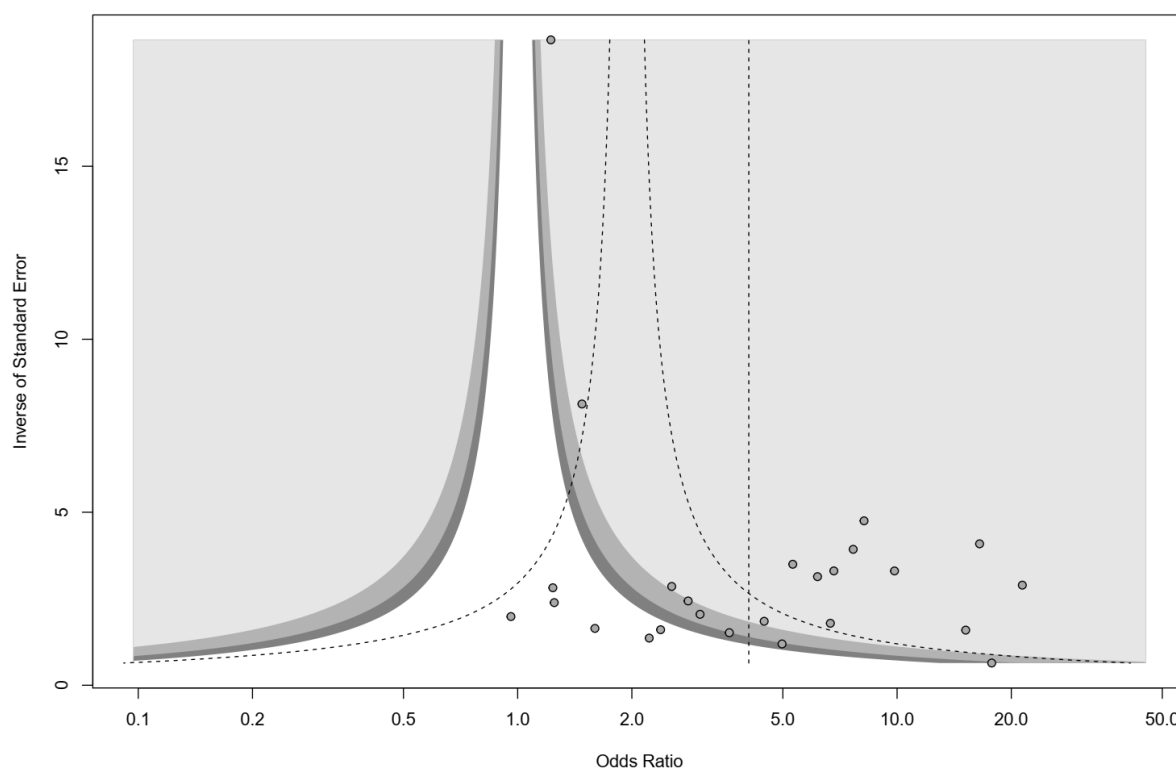
	Publication bias		Trim-and-Fill adjusted analysis		
	N studies	Harbord test	Odds ratio (95% confidence interval)	N studies	I ² , %
Case fatality rate	25	0.0009	1.28 (0.84-1.95)	43	95.6 (94.7-96.3)
Human Parainfluenza Virus	10	0.014	0.52 (0.31-0.87)	17	86.4 (79.7-90.9)
Human Metapneumovirus	12	0.029	0.46 (0.29-0.73)	19	69.2 (50.6-80.8)
Rhinovirus	9	0.329	Not necessary		
Enterovirus	5	0.384	Not necessary		
Human Bocavirus	4	0.414	Not necessary		
Influenza virus	13	0.477	Not necessary		
Human Adenovirus	10	0.663	Not necessary		
Human Coronavirus	4	0.870	Not necessary		
Respiratory Syncytial Virus	11	0.914	Not necessary		

Supplementary Table 6 : *Subgroup analysis for comparison of viral aetiologies of acute respiratory tract infections in Africa between HIV positive and HIV negative individuals*

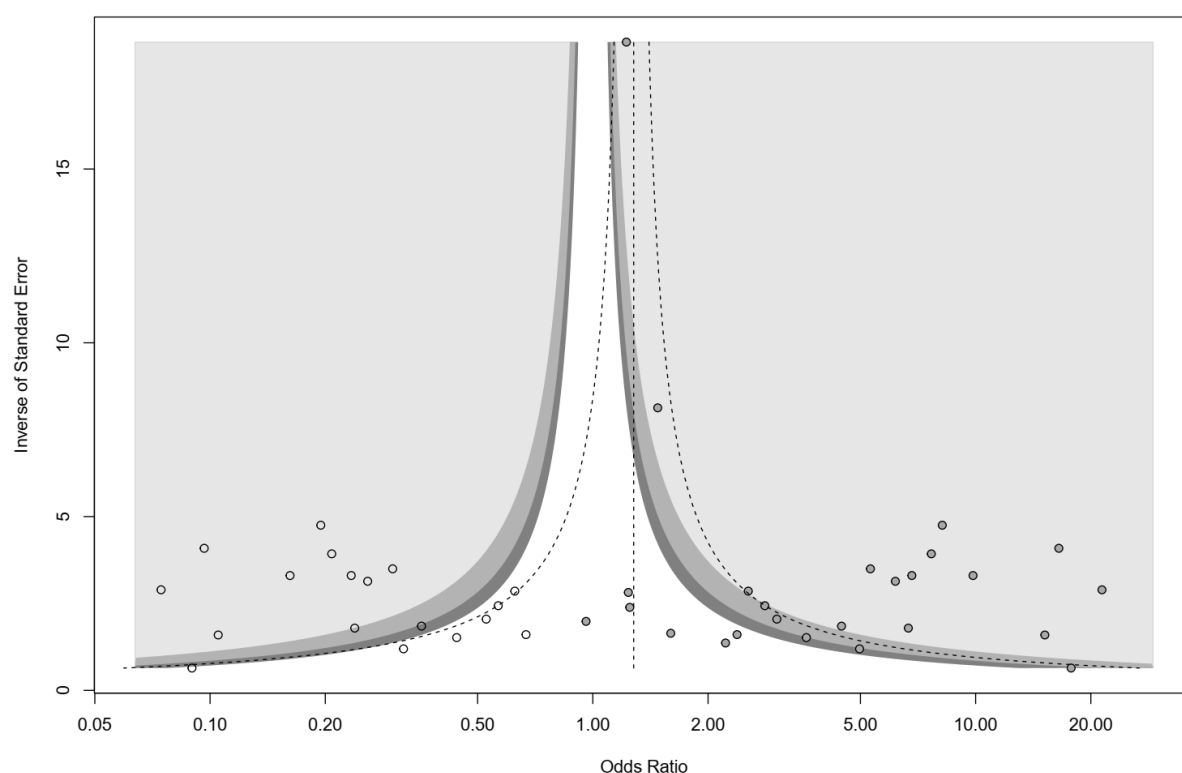
	Odds ratio (95% confidence interval)	N studies	I ² (%)	p difference
Rhinovirus				
<i>Age group</i>				
- Children	0.46 (0.25-0.83)	2	0.0	0.205
- Adults	0.26 (0.14-0.50)	1	-	
<i>Regions</i>				
- Eastern	0.66 (0.36-1.22)	2	0.0	0.890
- Southern	0.70 (0.48-1.02)	7	71.3	
Human Adenovirus				
<i>Age group</i>				
- Children	0.35 (0.17-0.73)	2	54.9	0.483
- Adults	0.71 (0.11-4.50)	2	86.0	
<i>Age group</i>				
- ≤ 5 years	1.00 (0.61-1.64)	4	7.4	0.0013
- > 5 years	3.91 (2.01-7.61)	1	-	
<i>Regions</i>				
- Eastern	1.10 (0.25-4.84)	3	87.2	0.531
- Southern	0.66 (0.37-1.18)	7	76.9	
Respiratory syncytial virus				
<i>Age group</i>				
- Children	0.30 (0.01-7.63)	2	97.0	0.780
- Adults	0.51 (0.08-3.27)	2	98.2	
<i>Age group</i>				
- ≤ 5 years	0.62 (0.31-1.26)	5	81.6	0.0002
- > 5 years	4.3 (2.09-8.87)	1	-	
<i>Regions</i>				
- Eastern	1.50 (0.58-3.89)	4	79.1	0.039
- Southern	0.40 (0.18-0.90)	7	95.0	
Human Bocavirus				
<i>Regions</i>				
- Eastern	1.13 (0.05-26.03)	2	84.6	0.796
- Southern	0.75 (0.49-1.13)	2		
Human Coronavirus				
<i>Regions</i>				
- Eastern	3.90 (0.63-24.16)	2	30.0	0.241
- Southern	0.81 (0.13-5.31)	2	93.8	
Human Parainfluenza Virus				
<i>Age group</i>				
- Children	1.60 (0.25-1.30)	2	84.9	0.554
- Adults	0.89 (0.51-1.56)	2	0.0	
<i>Age group</i>				
- ≤ 5 years	1.38 (0.73-2.62)	4	0.0	0.030
- > 5 years	4.05 (1.95-8.42)	1	-	
<i>Regions</i>				
- Eastern	4.01 (2.23-7.24)	3	0.0	< 0.0001

- Southern	0.69 (0.50-0.96)	7	34.9	
Influenza Virus				
<i>Age group</i>				
- Children	0.70 (0.36-1.35)	3	39.1	0.238
- Adults	1.39 (0.54-3.59)	3	66.3	
<i>Age group</i>				
- ≤ 5 years	0.45 (0.16-1.29)	3	24.3	0.251
- > 5 years	1.01 (0.41-2.47)	2	93.9	
<i>Regions</i>				
- Eastern	1.39 (0.90-2.15)	5	31.1	0.022
- Southern	0.76 (0.58-0.9966)	8	63.8	
Human Metapneumovirus				
<i>Age group</i>				
- Children	0.96 (0.32-2.88)	2	0.0	0.384
- Adults	0.52 (0.23-1.17)	2	10.5	
<i>Age group</i>				
- ≤ 5 years	0.46 (0.35-0.60)	6	0.0	< 0.0001
- > 5 years	3.00 (1.27-7.04)	1	-	
<i>Regions</i>				
- Eastern	1.50 (0.53-4.22)	3	46.8	0.037
- Southern	0.48 (0.38-0.61)	9	4.3	
Enterovirus				
<i>Age group</i>				
- Children	1.26 (0.37-4.22)	2	0.0	0.883
- Adults	1.51 (0.18-12.83)	1	-	
<i>Regions</i>				
- Eastern	0.76 (0.32-1.78)	4	49.5	0.272
- Southern	2.14 (0.42-11.01)	1	-	

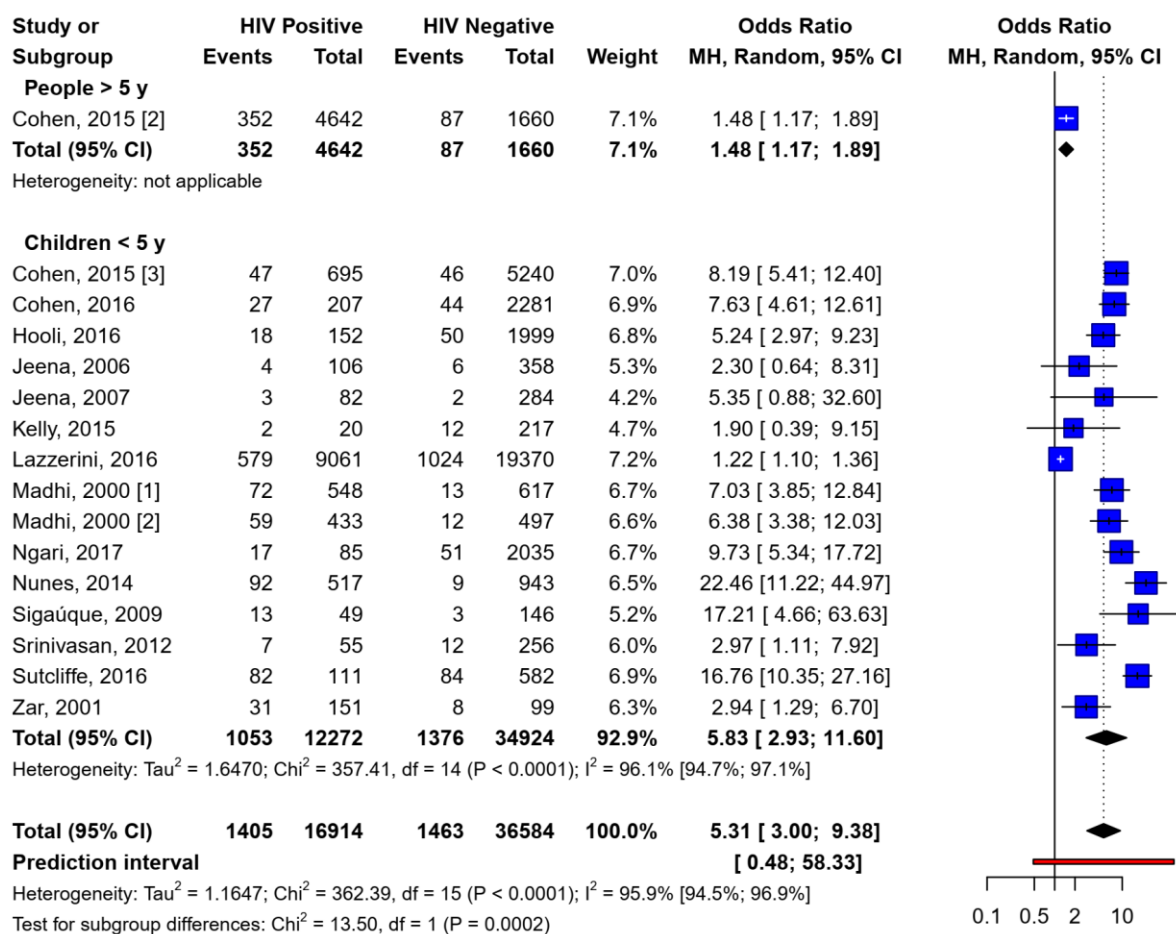
Supplementary Figure 1 : *Funnel plot for publication bias in comparison of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa*



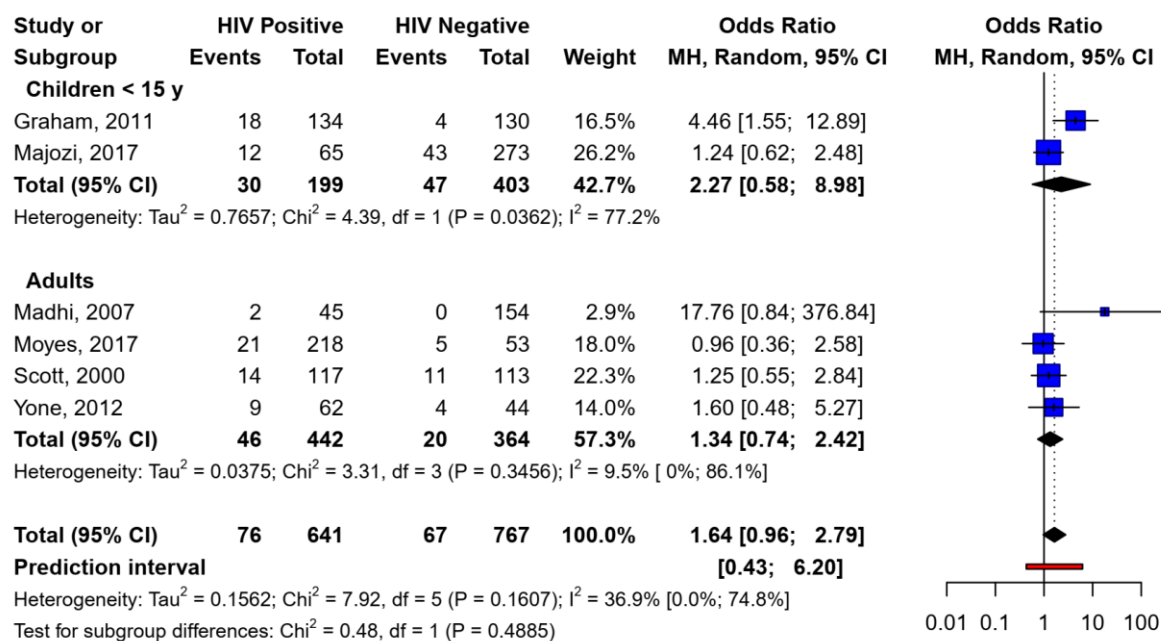
Supplementary Figure 2 : *Funnel plot for publication bias in comparison of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa, after Trim-and-Fill adjusted analysis*



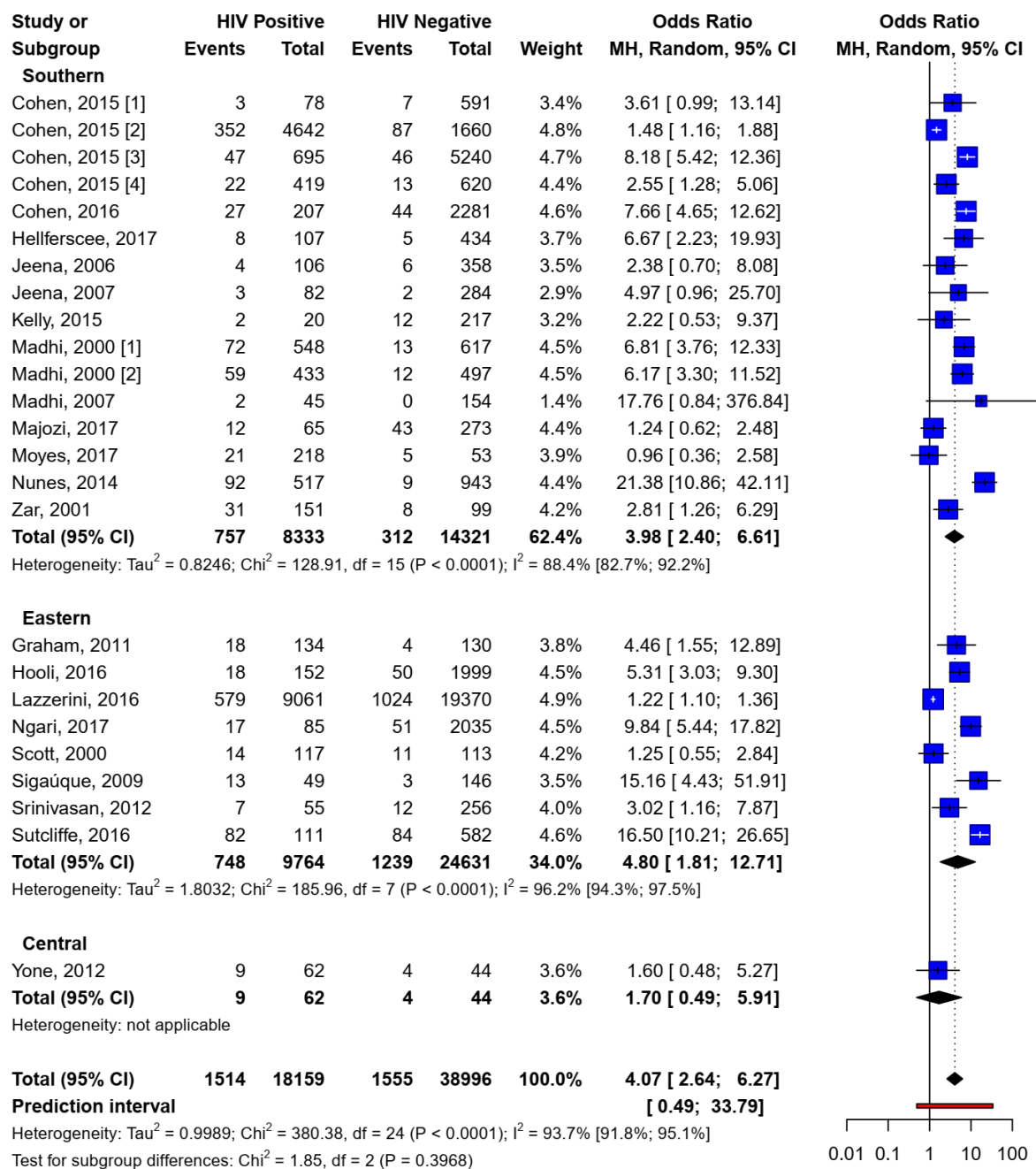
Supplementary Figure 3 : *Subgroup-analysis of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa: children aged ≤ 5 years versus people aged > 5 years*



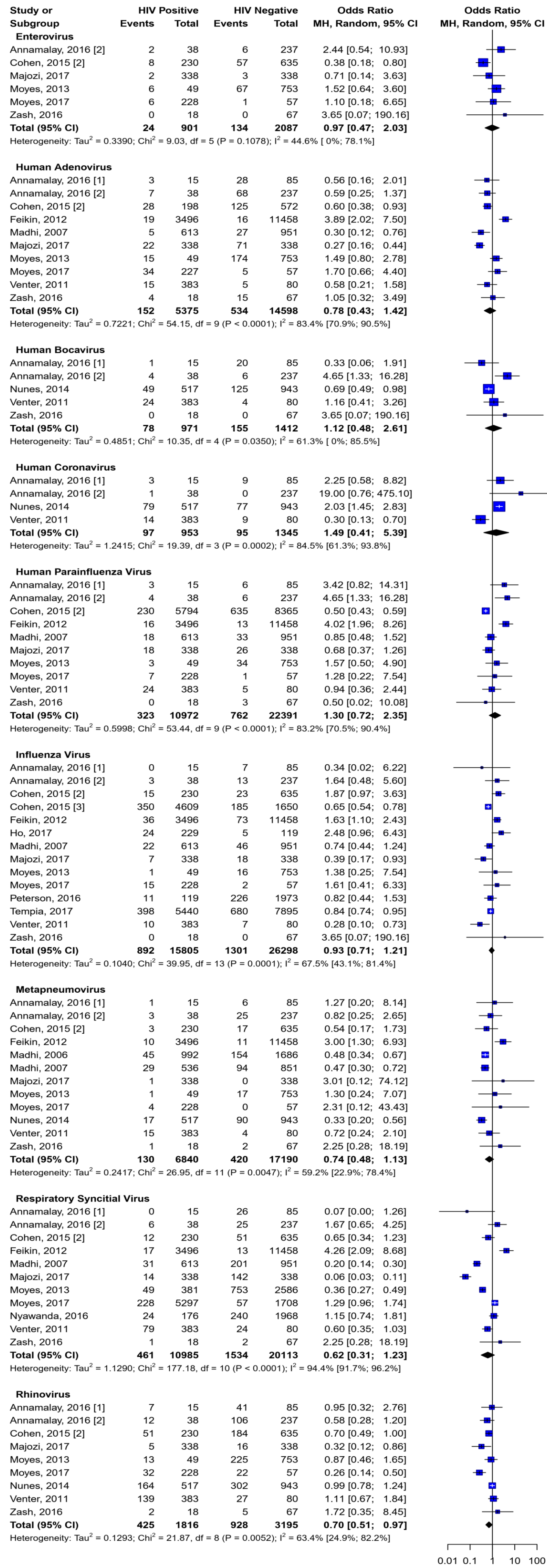
Supplementary Figure 4 : *Subgroup-analysis of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa: children (≤ 15 years) versus adults*



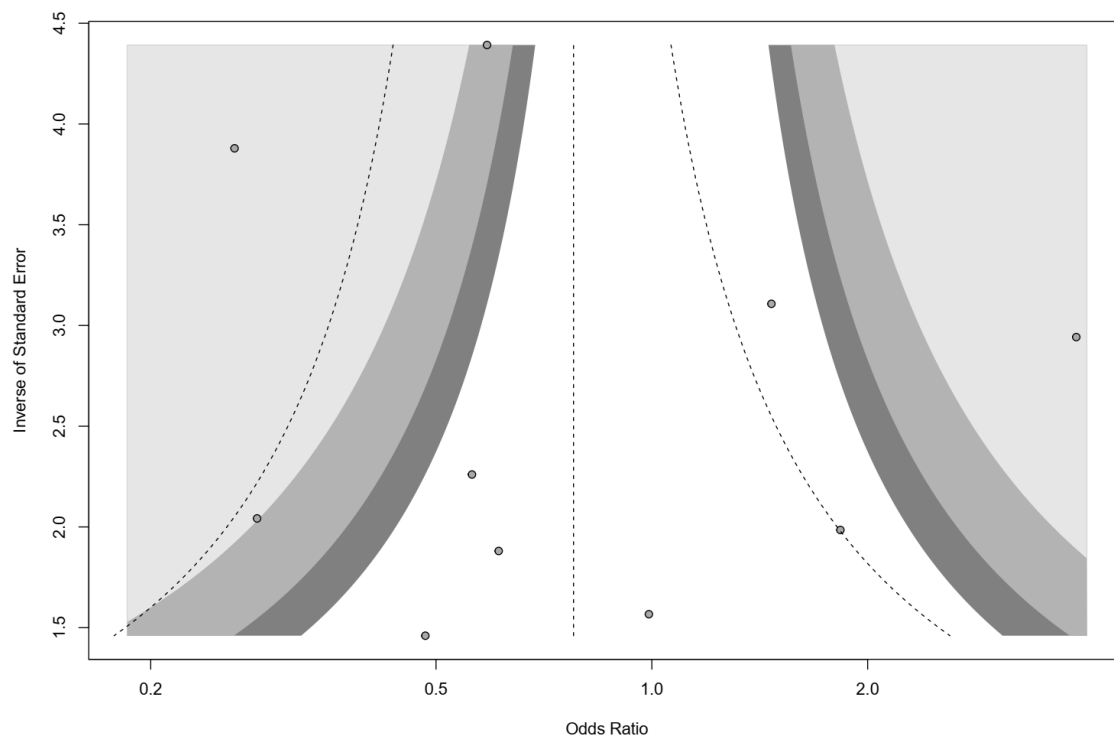
Supplementary Figure 5 : *Subgroup-analysis of case fatality between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa: by regions in Africa*



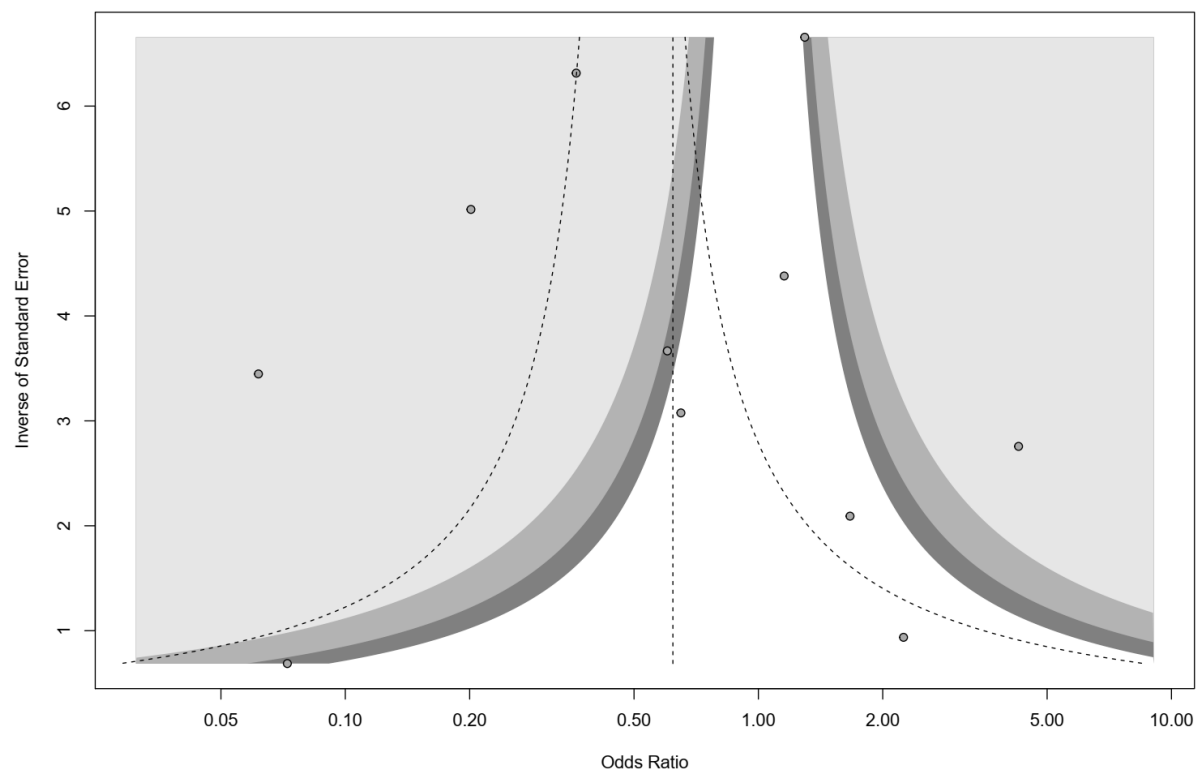
Supplementary Figure 6 : *Comparison of respiratory viral aetiologies of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa*



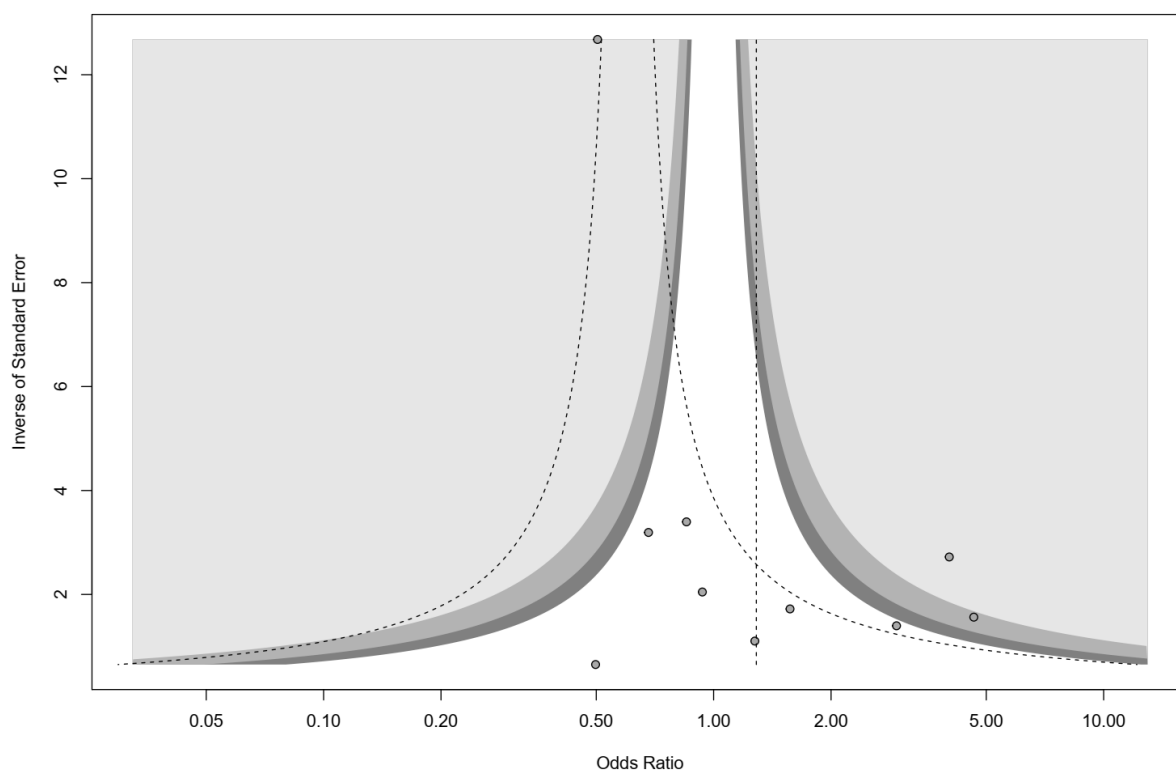
Supplementary Figure 7 : *Funnel plot for publication for comparison of Human Adenovirus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa*



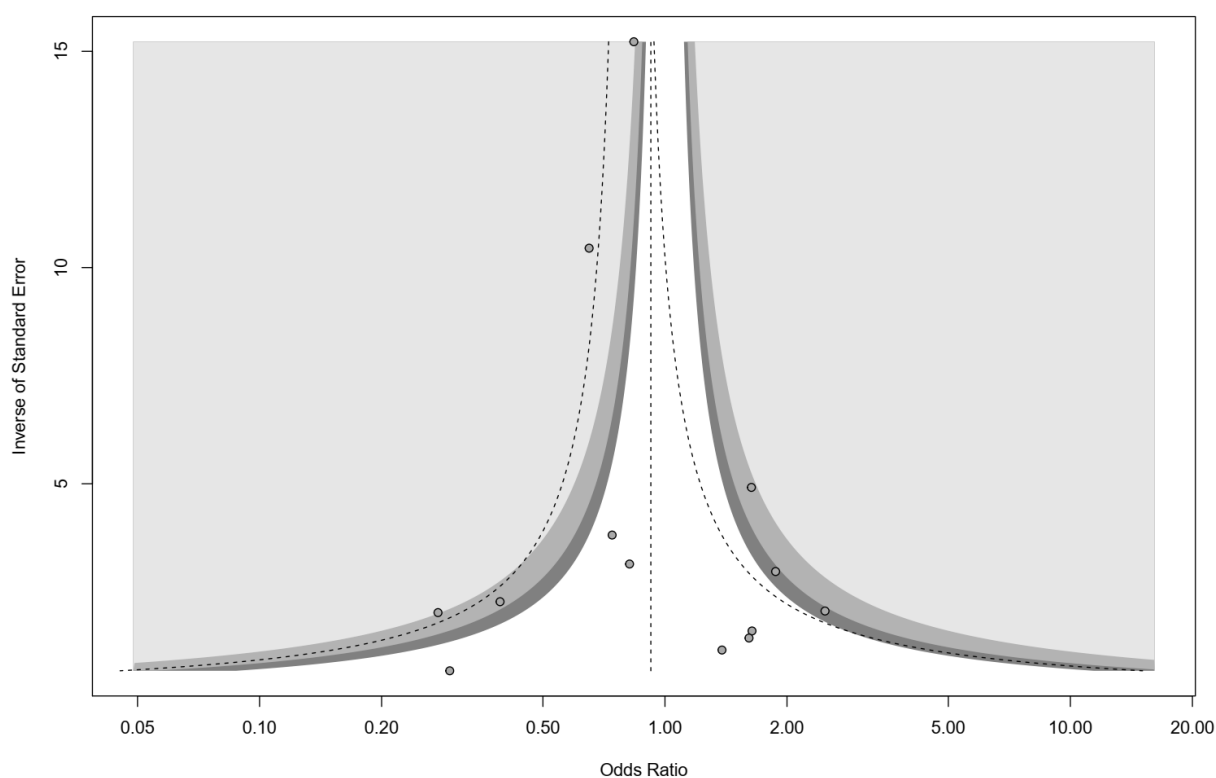
Supplementary Figure 8 : *Funnel plot for publication for comparison of Respiratory Syncytial Virus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa*



Supplementary Figure 9 : *Funnel plot for publication for comparison of Human Parainfluenza Virus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa*



Supplementary Figure 10 : *Funnel plot for publication for comparison of Human Influenza Virus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa*



Supplementary Figure 11 : *Funnel plot for publication for comparison of Human Metapneumovirus Virus as aetiology of acute respiratory tract infections between HIV-positive and HIV-negative populations in Africa*

